REVIEW ARTICLE

THE PHARMACOLOGICAL CLASSIFICATION OF CENTRAL NERVOUS DEPRESSANTS

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Not a few of the antihistamine drugs which appeared during the last half of the nineteen-forties made the patients so drowsy that they wondered whether perhaps the sneeze was the less disturbing. This fact became a challenge to theoretical and practical pharmacology. It was met in two ways. Some workers made antihistamines without this disturbing side-effect. Others found that it could perhaps be turned to good account, studied the effect, and tried to develop compounds without antihistamine activity but which possessed the special effect on the central nervous system of the antihistamines. The phenothiazine derivative promethazine was originated as an antihistamine and first made by Halpern in 1947[1]. Its pronounced sedative properties caused further investigations which led to chlorpromazine[2], the first and still one of the most important of the new psycho-sedative drugs. From the antihistamine substance diphenhydramine came captodiame[3], and from chlorcyclizine, hydroxyzine[4]. The anti-acetylcholine properties of some of the sedative antihistamines inspired the search which discovered benactyzine[5,6]. Two other routes also lead to this new field of pharmacology. One was the introduction of *Rauwolfia serpentina* and its alkaloids in Western medicine[7], and another was the synthesis of mephenesin by Berger[8]. The further search for compounds with the same effect as mephenesin eventually produced meprobamate[9], so popular in America. However, the initial clinical—and financial—success has had the effect that new compounds with sedative properties are still being synthesized and new drugs are appearing like mushrooms in an October forest.

The chemical formulae of the compounds arranged according to their effects and chemical constitution are given in the Tables I to VII. Many of these new sedatives act on the central nervous system in different ways and in many respects differ from the sedatives which were used before 1950. Some of them have properties in common with old and well-known compounds, others have properties hitherto undescribed. The whole field is becoming confusing for many pharmacologists and bewildering for many clinicians. Therefore, it might be useful to compare the actions of all these compounds, try to find out how they are mutually related, and make an attempt to classify them. This I have attempted to do.

The Pharmacological Basis of Classification

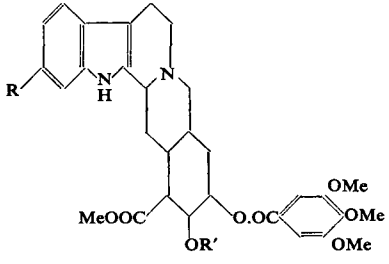
The Effect on Gross Behaviour

Most of the compounds decrease the spontaneous motor activity in quite small doses, but the differences in action become clearer when the doses are increased. After reserpine (Table I) and chlorpromazine

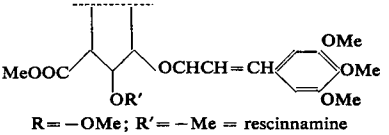
(Table II), the decreased spontaneous activity passes over into an immobility. The animals do not move spontaneously and if they are placed in bizarre and unusual positions they remain so for some time. But the righting reflexes are maintained even after the largest tolerated dose, and

TABLE I

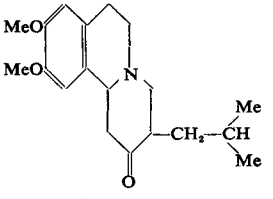
SOME INDIRECTLY ACTING MAJOR TRANQUILLISERS



R = —H; R' = —Me = dereserpine
R = —OMe; R' = —Me = reserpine



R = —OMe; R' = —Me = rescinnamine



Tetrabenazine

it is impossible to place mice or rats on their backs even if they are given near toxic doses of the compounds in question. An anaesthesia is never seen. For lack of a better word this reaction may be described, using an expression borrowed from psychiatry, as a cataleptic reaction.

Meprobamate and mephenesin (Table IV) give another type of reaction —flaccid paralysis. This is of central origin and distinguished from a curare effect by the fact that the monosynaptic reflexes are preserved. Some species of animal may show a complete flaccid paralysis without being anaesthetised.

The anaesthetic reaction is generally preceded by an increasing ataxia. This reaction is found after all hypnotics and most of the older sedatives.

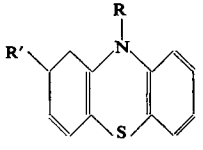
However, the mere observation of the gross behaviour is not sufficient to characterise the compounds. The effects on the more specialised functions of the central nervous system must also be considered. Many methods from neurophysiology and from psychology have been used in order to analyse and characterise the compounds.

The Spinal Level

Some compounds can abolish the spinal and medullar polysynaptic reflexes, for example the flexor reflex of the hindlimbs. With the same doses the monosynaptic reflexes, such as the knee jerk reflex, are unchanged. Also some medullar polysynaptic reflexes are inhibited in the same way, but it seems as if the intraneuronal processes in the forebrain

TABLE II

SOME MAJOR TRANQUILLISERS OF THE PHENOTHIAZINE GROUP



R	R′	Generic name
—CH_2·CH_2·CH_2·NMe_2	—H	promazine
— —	—O·Me	methopromazine
— —	—O·CON·Me_2	acetopromazine
— —	—Cl	chlorpromazine
— —	—CF_3	triflorpromazine
—CH_2·CH(CH$_2$·CH$_2$)N·Me	—H	mepazine
—CH_2·CH_2·CH_2N(CH$_2$·CH$_2$)N·Me	—Cl	prochlorperazine
— —	—CF_3	triflorperazine
—CH_2·CH_2·CH_2·N(CH$_2$·CH$_2$)N·CH_2·CH_2·OH	—Cl	chlorpiprozine, perphenazine

and in the midbrain are comparatively uninfluenced. This effect was first discovered and described as the main action of mephenesin[10] (Table IV). Since then, a long series of compounds have been synthesised which all have the same characteristic action of which meprobamate[11] and phenaglycodol[12] (Table IV) will be discussed as examples, later on. Other compounds with different chemical constitution, aminobenzoxazoles and aminobenzothiazoles[13] (e.g., zoxazolamine[14]) (Table V), also abolish the polysynaptic reflexes in the same way. Other spinal functions as well as the reflexes are abolished by these agents acting like mephenesin, for example the facilitation and inhibition of the knee jerk reflex seen after stimulation of higher centres[15].

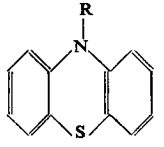
All compounds which show this inhibition on the spinal and medullar polysynaptic reflexes antagonise the effect of strychnine. They increase the threshold for the tonic seizures and considerably increase the lethal doses[10].

The Medullary Level

Many centrally acting compounds depress the medullary centres. Morphine is one good example among several which depress the respiratory centre. Others, like the barbiturates in high anaesthetic doses, have a paralyzing effect on the cardiovascular centre. The depression can be antagonised by a series of stimulating compounds like leptazol, picrotoxin, camphor, and the amphetamines. But these antagonisms are

TABLE III

SOME PHENOTHIAZINE DERIVATIVES



R = $-CH_2 \cdot CH_2 \cdot CH_2 \cdot NMe_2$ = promazine, (minor tranquilliser)
R = $-CH_2 \cdot CHMeNMe_2$ = promethazine (antihistamine, anti-emetic and minor tranquilliser)
R = $-CH_2CHMeNEt_2$ = ethopropazine (anti-Parkinsonism).

those of classical pharmacology and will not be described here. The compounds dealt with here have generally little influence on the medullary level. Exceptions are seen with chlorpromazine and its congeners which depress the trigger zone of the vomiting centre and in this way act anti-emetically[16,17]. Experimentally, this effect is demonstrated, by the antagonism of the compound to apomorphine. Most of the other compounds have little or no anti-emetic effect except hydroxyzine[18] (Table IIIA) and barbiturates in anaesthetic or subanaesthetic doses[19].

The Meso-diencephalic Level

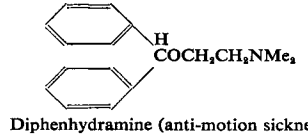
Many functions which have centres in the meso- and diencephalon are influenced. Firstly may be mentioned the dysfunction which results in motion-sickness. This state is presumably due to the disturbing influence of repeated vestibular impulses. The connection between the vestibular nucleus and the vomiting centre is not precisely known, but some compounds, for example diphenhydramine[20] (Table IIIA), are able to regulate the disturbance. In man, chlorpromazine does not act in this way in spite of its effect on the trigger zone of the vomiting centre[21].

A long series of other functions regulated by meso-diencephalic centres are inhibited by reserpine, chlorpromazine and related compounds. One of the most important is the centre or centres of the sympathetic nervous system. After administration of reserpine the tonus of this system is depressed showing myosis, ptosis, and bradycardia[22]. The effect of chlorpromazine on the sympathetic system is also depressing, but perhaps less pronounced. Here it is difficult to distinguish between the drug's peripheral anti-adrenergic action and a central depression of the sympathetic centres.

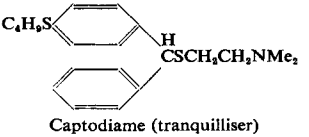
The autonomic centres of the cardiovascular system and those of heat regulation are also depressed. It has been clearly shown that the fall of blood pressure after reserpine is due to an action on meso-diencephalic centres[22–24]. But there has been some discussion whether the fall after chlorpromazine is caused by a central or a peripheral action since chlorpromazine has a strong peripheral sympatholytic action. However, an effect is seen in monkeys after intracisternal application of small doses

TABLE IIIA

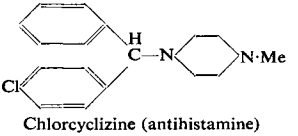
SOME MINOR TRANQUILLISERS AND CHEMICALLY RELATED COMPOUNDS
(Benzhydrol- and benzhydryl derivatives)



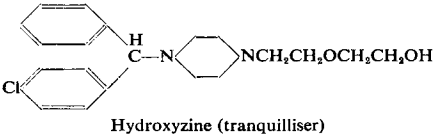
Diphenhydramine (anti-motion sickness)



Captodiame (tranquilliser)



Chlorcyclizine (antihistamine)



Hydroxyzine (tranquilliser)

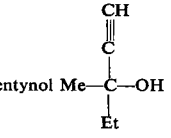
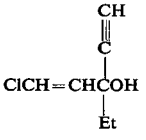
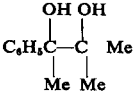
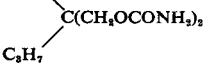
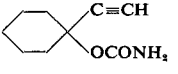
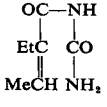
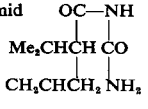
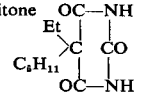
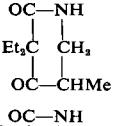
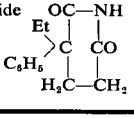
of chlorpromazine, which suggests at least a partial central action[25]. Reserpine and chlorpromazine also inhibit the centre for heat regulation causing a decrease of the body temperature when the external temperature is below the body temperature[16,26] and an increase when it is above. Hydroxyzine has a similar effect[18], but most other psycho-sedatives have little or no influence on the heat regulation.

The so-called sham rage is a state which causes violent outburst of all sympathetic functions. It can *inter alia* be provoked in decorticated cats. This state is suppressed by chlorpromazine[27] and reserpine[28], actions which might be connected with the general effect on the sympathetic system.

Many hormonal functions are also disturbed after chlorpromazine and reserpine, functions which are not easy to study in animal experiments, and our knowledge rests on clinical observations only. Patients treated with chlorpromazine or reserpine often show a formidable increase in appetite and gain considerably in weight. Disturbances of the menstruation, and even lactation in female patients who are not or never have been

TABLE IV

SOME TRANQUILLO-SEDATIVES AND HYPNO-SEDATIVES

No.	Generic name	Hypnotic	Sedative	Inhibiting polysynaptic reflexes
I	Ethanol EtOH	+	+	O
II	Methylpentynol 	+	+	O
III	Ethchlorvynol 	+	+	O
IV	Phenaglycodol 	+	+	+
V	Mephenesin *o*-$MeOC_6H_4OCH_2CHOHCH_2OH$	O	O	+
VI	Reorganin *o*-$MeC_6H_4OCH_2CHOHCH_2OH$	O	O	+
VII	Urethane $MeCH_2OCONH_2$	(+)	O	O
VIII	Meprobamate 	(+)	+	+
IX	Ethinamate 	+	+	O
X	Ectylurea 	(+)	+	O
XI	Sedormid 	+	+	O
XII	Pentobarbitone 	+	+	
XIII	Methyprylone 	+	+	O
XIV	Glutethimide 	+	+	O

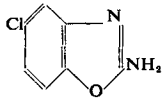
pregnant, have also been described after reserpine. All these observations may be interpreted as an influence of the drugs on the hypothalamic centres regulating the hormonal system.

The Extrapyramidal System

The extrapyramidal system is the name for all motor functions not belonging to the pyramidal tracts. In man, disturbances of the extrapyramidal system are manifested through Parkinson's syndrome with muscular rigidity and a characteristic tremor. The functions of clinical importance regulating the extrapyramidal system are located in di- and mesencephalon, but neurophysiological experiments in animals have shown that centres influencing the motor system are found in the cortex,

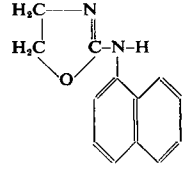
TABLE V

TWO COMPOUNDS NOT CHEMICALLY RELATED TO MEPHENESIN, BUT INHIBITING POLYSYNAPTIC MEDULLAR REFLEXES



(I)

(I, zoxazolamine, no sedative effect, no hypnotic effect)



(II)

(II, 2-(1-naphthylamino)2-oxazoline, tranquillising effect)

cerebellum and many other parts of the central nervous system. Parkinson symptoms are the most common side-effects seen during the clinical use of chlorpromazine and reserpine. The symptoms are very similar to those described by von Economo during the epidemic encephalitis after the first World War and shown to be due to pathological changes in the meso- and diencephalic centres. There is a slight difference between the effect of chlorpromazine and reserpine, the Parkinsonism after the first is more characterised by rigidity, after the latter by tremor and restlessness[29]. Extrapyramidal symptoms are also provoked in animals, especially monkeys by, for example, reserpine[30]. The symptoms in man and animals disappear when the drug is discontinued.

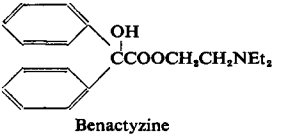
The agents used in the clinic for Parkinsonism are able to ameliorate the extrapyramidal symptoms provoked by reserpine and chlorpromazine. Some of these compounds are chemically and pharmacologically closely related to chlorpromazine, for example, ethopropazine and diethazine. Only slight changes in the molecule are necessary to change a compound from one provoking Parkinsonism to one able to depress the symptoms of Parkinsonism (Table III). It would seem that these compounds are bound to the same or nearly the same elements in the central nervous system, and that their capacity to provoke or improve Parkinsonism depends upon their capacity to inhibit or stimulate these elements. Diphenhydramine[31] and some derivatives, mephenamine[32] (with a tolyl-group replacing a

phenyl-group) and Rigidyl[33] (with a diethylamino-group) are also clinical effective anti-Parkinsonism agents.

The Meso-diencephalic Reticular System (Arousal Syndrome)

The reticular system is an anatomically poorly defined structure described as "all grey masses of the tegmentum of the medulla, pons and midbrain which do not belong either to the cranial nerves, to the relay nuclei of the cerebellar system or to the relay nuclei of the lemniscal systems"[34]. To a part of this reticular system is ascribed a function in the extrapyramidal system and this is called the descending reticular system.

TABLE VI

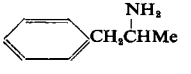


Benactyzine

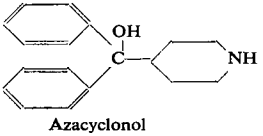
Another part, the ascending reticular system, belongs to the sensory pathways of the central nervous system[35]. The impulses received through the sensory apparatus are not only carried directly to the specific localised areas in the sensory cerebral cortex, but they also pass through side branches into the reticular system. Here they are transformed and transmitted diffusely over the whole cortex. The electric activity of the cortex of, for example, the cat or the rabbit not receiving these diffuse

TABLE VII

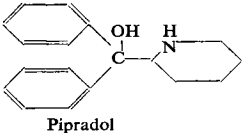
THE AMPHETAMINE–PIPRADROL GROUP



Amphetamine



Azacyclonol



Pipradol

impulses is characterised by slow waves with large amplitudes. This resting pattern is changed to one with fast waves of considerably smaller amplitudes when the reticular system is stimulated by a sensory impulse. This effect is called the EEG arousal reaction. The constant inflow of diffusely spread impulses from the reticular system seems to be connected with the state of consciousness so that a cortex which does not receive these impulses is incapable of perception.

Some of the compounds have no influence on the EEG arousal reaction, mephenesin is an example. The mere suppression of the polysynaptic reflexes has thus no relation to the function of the reticular system[36,37].

Chlorpromazine and its congeners incompletely inhibit the arousal reaction. After these drugs a stronger stimulation is necessary to provoke a reaction and its duration is shorter. But still some effect can be seen

even when the doses are increased so much that other factors influence the EEG[38,39]. A complete inhibition of the arousal syndrome is found after barbiturates[36,40] and other hypnotics and anaesthetics. This inhibition is closely connected with the loss of consciousness. Similarly meprobamate depresses the reaction[19].

Other compounds completely block the EEG arousal effect so that it cannot be provoked even by the strongest stimulation. This effect is seen after the anti-acetylcholines with a central effect; hyoscine, atropine[41] and benactyzine[42,43] (Table VI). Diphenhydramine and similar compounds also show the same blocking effect which is attributed to their anti-acetylcholine effect[41]. The abolition of the arousal syndrome after these compounds is seen without any of the loss of consciousness observed after the anaesthetics. In spite of a constant resting EEG pattern, the animals behave normally and react normally to various impulses. The blocking of the EEG arousal is not linked to any special central effect characteristic of the different compounds of this group[44]. Atropine and benactyzine have the same influence on the EEG, but their psychic effects differ considerably. Some authors suggest that this EEG effect is connected with the anti-Parkinsonism effect of the compounds[41].

Some substances provoke the EEG arousal syndrome. Acetylcholine itself and agents acting like acetylcholine are examples, and the centrally acting anti-acetylcholines are able to abolish this effect[41]. Adrenaline and other sympathomimetics including the amphetamines and pipradrol are also able to provoke the EEG arousal syndrome[43]. All these compounds give a hyperexcitability and restlessness corresponding to a super-awake state. Lysergic acid diethylamide (LSD) facilitates the formation of the arousal pattern[45]. This effect might be connected with the general stimulation of the sympathetic centres by LSD, but other mechanisms are presumably involved.

The effect of reserpine is paradoxical. Administration gives an arousal EEG pattern[46,47], in spite of the fact that the animals are heavily sedated.

Azacyclonol (Table VII) has no effect except in large doses where it provokes arousal[41], but it is able to restore the normal arousal pattern enhanced by lysergic acid diethylamide and mescaline[48]. It has no effect on the arousal syndrome after amphetamines or its progenitor pipradrol. The antagonising effect of azacyclonol on the LSD-arousal is not specific. The same antagonism is also seen after many other sedatives, including chlorpromazine.

Other EEG Effects

The other effects on the electrical activity of the brain are not all thoroughly investigated, but some light has been thrown on the difference between one group and another.

In addition to the already mentioned arousal effect, what is called the primary localised response, and the recruiting response also belong to the sensory system.

The primary localised response is the short brain potential found localised in the area of the sensory cortex corresponding to the region

which has been stimulated. The impulse follows the classical lemniscal pathways described in every textbook of physiology. This response is remarkably uninfluenced by any of the drugs; barbiturates, even in anaesthetic doses[39,40,49,50], benactyzine[51], mephenesin[52], chlorpromazine[39,53] or reserpine[53].

The recruiting response of the cortex is seen when the anterior thalamic part of the reticular formation is stimulated electrically with frequencies similar to those of the spontaneous rhythms of the cortex. It consists of a successive increase in amplitude of the cortical response found diffusely over great areas of the cortex, and is called recruiting, because more and more neurones become involved. The recruiting response cannot be provoked in a cortex which gives the arousal syndrome, and therefore the effect of compounds giving such a reaction cannot be studied. Some true anaesthetics depress the recruitment, for example, ether[52], but the barbiturates enhance it considerably[39,40,49,50]. Benactyzine has no effect[51] nor has reserpine[53]. A slight inhibition is found after mephenesin[52]. No statement can be found for meprobamate. Finally, small doses of chlorpromazine facilitates the recruiting response while larger doses inhibit it[53].

The spontaneous electrical activity (EEG). The spontaneous electrical activity pattern after ether or barbiturate anaesthesia, or sleep, and the suppression of the α-waves after stimulating drugs has been frequently described. After moderate doses of reserpine, chlorpromazine, the minor tranquillizers, meprobamate, mephenesin, and azacyclonol no effect is seen on the human EEG. Benactyzine forms an exception in being able to suppress the α-waves[55].

In animals the spontaneous electric activity is mainly regulated from the reticular system and the effects of the compounds giving resting or arousal syndromes have been described already. With larger doses other electrical activities may dominate. Such activities start at different parts of the central nervous system according to the type of agent, and may perhaps help to characterise the mode of action of the compound. A regular continuous activity starts in the hippocampus after reserpine[53,56,57]. After chlorpromazine in fairly large doses, seizure-like discharges begin in the amygdala and spread to the rest of the brain with increasing doses[39]. The depressing effect of the barbiturates is first seen in cortex and the caudate nucleus in doses which leave the thalamus and hypothalamus unaffected[52]. Meprobamate gives a synchronisation of the electric activity showing 10–20 c/s waves beginning in the thalamic centres and spreading from there to the cortex[58].

The two neuron intercortical system. An electric stimulation applied to a point in, for example, the optic cortex evokes a response in the connecting symmetrical point in the contralateral cortex. This response is inhibited by a series of stimulating agents; adrenaline, noradrenaline, mescaline, LSD, bulbocapnine and 5-hydroxytryptamine. The inhibiting effect of mescaline is abolished after azacyclonol, reserpine and chlorpromazine[59].

Nicotine convulsions. Intravenous administration of nicotine to rabbits give EEG changes characteristic of a grand mal seizure. A series of

compounds, caraminiphen, ethopropazine, chlorpromazine, trihexyphenidyl, promethiazine, diphenhydramine, chlorcyclizine and pyrilamine, most of these being anti-Parkinsonism drugs (except, as we have seen, chlorpromazine), are able to antagonise this effect[60,61].

Electric stimulation of the brain with liminal voltage. Electric stimulation of this kind gives a discharge occurring during the stimulation and an after-discharge outlasting the stimulus. Meprobamate increases the threshold for the first reaction and most antiepileptics the threshold for the second[57,62].

The effects of the differing types of the psychotropic compounds on the electric activity of the brain may help to characterise them. However these effects give little information on the understanding of the mode of action of the compounds. So far, it has been difficult to correlate the changes of the EEG and the neurophysiological and behavioural changes after administration of the compounds, but it is to be hoped that the intense research being made in this field will throw more light on the problems.

The Psychic Level

The psychic effect of the compounds on animals is studied by assessing their reactions to standardised impulses. These reactions may be classified in groups; the unlearned reactivity, the learned reactivity, the stress induced behaviour, and the capacity for solving problems. The influence of the psychotropic agents on the last named capacity has been little examined and is of limited interest in this context. It will therefore not be discussed.

Unlearned Reactivity

The unlearned reactivity is the innate response to certain impulses which is characteristic for each species. Some of these reactions are simple and may perhaps be compared with mere reflexes. Others, in the form of instincts may be extremely complicated "chain-reactions". A few examples will be mentioned.

The calming effect of the compounds on the natural aggressive-defensive behaviour of monkeys is frequently described under the name of the "taming" effect. This taming is seen after reserpine[22], meprobamate[11], and to a minor degree after chlorpromazine[63]. Other compounds, such as barbiturates and benactyzine[51], have no effect. The same compounds seem to have a similar effect on the fighting instinct of the male Siamese fighting fish (*Betta splendens*)[64].

Another form of unlearned reactivity is the so-called orientating reflex. The somatic behaviour of a dog when it is exposed to an unknown and unexpected signal is well known to every dog-owner. Less well known is the fact that autonomic reactions also occur, for example, in the form of a temporary increase in the pulse rate. Chlorpromazine and reserpine are able to abolish the somatic and autonomic orientating reflexes[65]. Barbiturates[66] and alcohol[67] never completely abolish the orientating reflexes unless the animals are fully anaesthetised.

Some further examples of more complicated innate behaviour have been investigated, but only the effect of one or two types of agents have been examined. For this reason the results are difficult to compare. However, it seems that if an agent has an inhibiting influence on one type of innate behaviour, it also inhibits other types of innate behaviour. Naturally, quantitative variations from test to test are found, and reservations must be made for new discoveries in this field.

Learned Behaviour

The learned behaviour includes all conditioned reactions and other forms of trained behaviour. The methods applied have varied from classical Pavlovian experiments on conditioned reflexes to the study of complicated reactions learned by the animals in order to avoid a disagreeable stimulus or to obtain a reward. The influence of the compounds on the learned activity seems to be so constant from method to method that it is unnecessary to distinguish between the different methods here.

The learned activity is inhibited by reserpine[65,68–71], chlorpromazine[65,70–72], and barbiturates[66]. After reserpine and chlorpromazine only the somatic, but not the autonomic reaction disappears[65]. The author, together with Sonne, has observed that meprobamate seems to have no effect in the few experiments made. In contrast to the other compounds, benactyzine increases the number of conditioned responses[73] and decreases the latency time of the somatic conditioned reaction.

Some drugs have a stronger influence on the unlearned activity than on the learned activity. The orientating reflex disappears after doses of chlorpromazine and reserpine which preserve the conditioned reflexes[65]. The autonomic response in the form of the increased heart rate disappears during the orientating reflex, but can never be brought to disappear completely in the conditioned response. On the other hand, other drugs have a stronger influence on the unlearned reactivity. After alcohol and barbiturates the orientating reflexes may be detected at stages where the conditioned reflexes have disappeared completely[66,67]. Unfortunately not all compounds have been examined with the same technique so that a complete comparison cannot be made.

Stress-induced Behaviour

Animals exposed to a mental stress will show a characteristic behaviour varying with the species and the experimental situation. The classical mental stress-induced behaviour is the so-called experimental neurosis. Animals exposed to situations to which they do not know how to react show a well-defined behavioural pattern for which Pavlov coined the word "experimental neurosis". For example, cats placed before a box, which might contain food or might have fear-inducing properties, react to the situation with a characteristic somatic behaviour and might also show some autonomic symptoms, like vomiting and diarrhoea[74,75]. Administration of barbiturates[76], alcohol[74], meprobamate (author, unpublished results)

and especially benactyzine[77] has a normalising influence on these conflict-induced behavioural patterns in cats or monkeys.

The stiffened, tense behaviour of rats expecting the sound signal to which they have to react in order to avoid an electric shock is abolished and normalised by benactyzine[78] and meprobamate (author, unpublished results).

The general depressive effect of chlorpromazine and reserpine are such that a different technique must be applied to demonstrate the effect of these compounds. In such experiments reserpine has an improving effect on a psychic stress situation although the normal performance is considerably inhibited[79].

Self-stimulation

Until recently there has been a wide gap between the pharmacological investigations based on neurophysiological methods and those based on the methods of animal and human psychology. This gap is now beginning to be closed. Electric stimulation applied to specific hypothalamic and palaeocortical structures of the rat brain has the same effect as an anticipated effective reward[80]. Bipolar electrodes are chronically implanted in the brains of rats who rapidly learn to stimulate themselves by means of a lever-contact placed within the cage. The frequency of lever pressing is an expression of the force of the drive with which the animal seeks this peculiar form of a reward. Rates of as much as 80 responses per minute are found. This lever pressing rate is influenced by some of the psychotropic agents. Thus the rate is decreased after reserpine, chlorpromazine and pentobarbitone, but the different drugs have different effects according to the site of the implanted electrodes[81,82]. The further development of this technique seems to give promise of localising the site of these drug effects and thus provide a further basis for their classification.

Antagonisms, Synergisms and Potentiation

When given together, two psychotropic agents may act antagonistically or synergistically. As a rule the depressing agents antagonise the stimulating agents and *vice versa*, but this rule is not without exceptions.

The property of mephenesin and similar agents to antagonise strychnine has already been mentioned. However, if a compound antagonises strychnine it does not necessarily antagonise the effect of other convulsants. In comparison with mephenesin, meprobamate antagonises leptazol more than it does strychnine[11], and some oxazoline derivatives have been found which antagonise strychnine without affecting leptazol convulsions. The same compounds which antagonise leptazol generally also increase the threshold for electro-convulsive seizures (the liminal voltage, mentioned earlier), but the two effects do not run absolutely parallel[83]. It is well known that the anti-epileptics also are capable of antagonising leptazol and electro-convulsions, but neither meprobamate or mephenesin have an effect on epilepsy similar to that of the true anti-epileptics. Chlorpromazine has no effect on the strychnine, picrotoxin, cocaine[84] and leptazol convulsions[85], nor has reserpine[86–88]. The

TABLE VIII

		Reserpine	Chlorpromazine	Diphenhydramine	Hydroxyzine	Pentobarbitone	Phenaglycodol	Meprobamate	Mephenesin	Benactyzine	Azacyclonol	Pipradol	Amphetamine	Mescaline	Lysergic acid diethylamide
General effects	Polysynaptic reflexes	O	O	O?	O?	O	–	–	–	O	?	?	O	O	O
	Convulsions after electrostimulation	+	+	?	?	–	–	–	–	±	?	?	?	?	?
	" " strychine	O	O	O?	O	i	–?	–	–	?	?	?	?	?	?
	" " leptazol	–	O	?	?	–	–	–	–	?	?	?	?	?	?
	" " nicotine	?	–	—	—	O	?	O?	O?	?	?	?	?	?	?
Gross behaviour	Spontaneous activity	–	–	+	–	–	–	–	–	+	–	+	+	+	+
	Catalepsia	+	+	O	O	O	O	O	O	O	O	O	O	+	O
	Paralysis	O	O	O	(+)	O	+	+	+	O	(–)	O	O	O	O
	Anaesthesia	O	O	O	O	+	+	e	O	O	O	O	O	O	O
	Convulsions	O	e	+	O	O	O	O	O	e	e	O	O	O	O
Synergism or antagonism	Anaesthetics and hypnotics	+	+	+	+		+	+	(+)	+	+	–	–	–	–
	Amphetamine	–	–	?	–	–	–?	–?	?	O	–			+?	+?
Lower centres	Vomiting	O	–	(–)	–	i	O	O	O	O	O	O?	O	(+)	(+)
	Motion sickness	O	O	–	–?	i	O	O	O	O	O	O?	O	O	O
	Blood pressure	–	–	O?	O	O	O?	O	O	O	O	O	+	±	+
	General sympathetic tonus	–	–	O?	O	O	O?	O	O	O	O	O	+	(+)	+
	Body temperature	–	–	O?	–	i	O?	O	O	O	O	?	+	+	+
	Appetite	+	+	O?	O	O	O?	O	O	O	O	O	–	–	(–)
	Endocrine centres	±	±	?	O	O	O	O	O	O	O	?	?	?	?
Extra pyramidal system	+Disturbing equilibrium –Regulating	+	+	–	–?	O	O?	O	O	(–)	O?	O?	O?	O?	+

TABLE VIII—*continued*

EEG	Recruiting	O	(±)	?	?	+	+	−?	—	O	?	?	?	?	?
	Arousal	+	(−)	−	−?	—	(−)	—	(−)	−	O +	+	+	+	+
	Two neuron intercortical	normal-ising	normal-ising	?	?	−	?	?	?	?	normal-ising	(−)?	−	−	−
	α Waves in normal EEG	O	O	O	O	spind-les	?	O	O	−	O	O	(−)	(−)	(±)
Higher psychic functions in animals	Unlearned reactivity	−*	−*	O	O?	−	−	−	O?	O	O	?	+	O	?
	Avoidance reaction: motor	−	−	O	−	−*	?	O	O?	+	O	?	±	O −	−
	" " : autonomic	O	O	O	O	−*	?	?	O?	?	O?	?	?	(+)* −	?
	Reward reaction	−*	−*	O	O	−*	?	?	O?	±	O?	?	+	?	?
	Stress or conflict-induced behaviour	O −	O	O	O	O −	?	−	O?	−	O?	?	?	?	?
	Fatigue	?	?	?	?	?	?	?	?	?	?	−	−	−	−
Higher psychic functions in man	Emotional impression of disturbing stimulus	−	−	O −?	−	(−?)	−	−	?	−	(−)?	O	O	(−)	(−)
	Euphoria	O	O	O	?	O(+)	O	O(+)	O	O	O	O	+	±	±
	Thought blockade	O	O	(e)	?	O	O?	O	O	+	O	O	O	(+)	(+)
	Distorted sensual perception	O	O	O	O −	O	O	O	O	O	O	O	O	+*	+*
Basic actions of possible importance	Acetylcholine	O	−	−	−	O	O	O	O	−	O	O	O	?	O
	Adrenaline	(−)	−*	O	(−)	O	O	O	O	O	O	O	+	+(?)	−
	5-Hydroxytryptamine	O	O	O	?	O	O	O	O	−	O	O	?	?	−*
	Local anaesthetic effect	O	+	+	+	O	O	O	O	+	O	O	O	O	O
	Release of 5-hydroxytryptamine	+*	O	O	O?	O	O	O	O	O	O	O	O	O	O

Key.—O, no effect; +, enhancement, lowering of threshold, synergism; −, inhibition, increase of threshold, antagonism; ( ), incomplete effect; i, inhibition in large doses; e, enhancement in large doses; ?, lack of information; *, dominating effect; ±, O̲, etc., effect depending on the experimental conditions.

hyperactivity induced by amphetamine—which never ends in convulsions —is antagonised by barbiturates, chlorpromazine, and azacyclonol, but not by reserpine.

Very characteristic for all the recent sedatives is their property to potentiate the effect of anaesthetics of which hexobarbitone and alcohol are the most commonly used in such experiments. This effect was discovered by Winter with diphenhydramine[89]. As mentioned, most of the compounds are not anaesthetics *per se*, and some give even hyperactivity in moderate—and convulsions in larger—doses. This anaesthesia-prolonging property is common to almost all the more recent sedatives[90,91], but it is not found with every depressant of the central nervous system, for example, not with morphine[91].

Some Typical Groups

From this analysis it is seen that the depressants differ in their action upon the single functions of the central nervous system. When all these actions are tabulated as in Table VIII, it is possible to distinguish a "profile of action" which is characteristic for each agent. Drugs with similar profiles of action may be collected into groups.

The Major Tranquillizers

This group consists of reserpine (and some other active rauwolfia alkaloids) and chlorpromazine with its more recent congeners. The major tranquillizers are mainly characterised by their depressive effect on the lower centres, including the extrapyramidal system. They give a cataleptic reaction in gross behaviour. Psychically, they have a greater influence on the unlearned behaviour than on the learned behaviour.

Although reserpine and the reserpine-like alkaloids on one side and chlorpromazine and its congeners on the other side have many properties in common, one fundamental difference is found in their mode of action. Reserpine does not act directly on the cells of the central nervous system. After administration of reserpine, 5-hydroxytryptamine[92–94] and the catecholamines[95] disappear from the central nervous system. The symptoms observed follow closely the changes of the amine-concentration, not the concentration of reserpine in the brain or the tissues[96]. It is therefore reasonable to assume that the effect of reserpine is closely connected with the deprivation of the amines, although their precise function in the central nervous system is not clear. A further proof of this conception is the effect of reserpine on animals pretreated with iproniazid (Marsilid, 2-*iso*propyl-1-*iso*nicotinyl hydrazide) an antituberculosis agent. The compound is a potent and irreversible inhibitor of monoamino oxidase, an enzyme which *inter alia* deaminates noradrenaline, adrenaline, and 5-hydroxytryptamine. When animals are pretreated with iproniazid and given reserpine, they are not sedated, but become hyperactive and show symptoms similar to those seen after LSD or amphetamines with a general stimulation of the sympathetic system instead of an inhibition[93,97]. Furthermore, the content of 5-hydroxytryptamine and presumably also that of catecholamines shows very little

decrease after reserpine when the animals are pretreated with iproniazid[98]. Apart from reserpine and two other rauwolfia alkaloids, dereserpine and recinnamine[99], other compounds, chemically unrelated to reserpine, are found to have the same effect. The best known is tetrabenazine (Table I)[98]. It has also the same pharmacodynamic and biochemical effect as reserpine but is shorter acting.

Chlorpromazine has no effect on the amines, and its pharmacodynamic effects cannot be modified by iproniazid. Hence, it must have a mode of action different from that of reserpine. Some examples of differences between reserpine and chlorpromazine have been mentioned previously, but the similarity in the action of reserpine and chlorpromazine is more striking than the differences. This fact suggests that both exert their effect on the same parts of the brain. The aminocatechols[100] and 5-hydroxytryptamine[98] are found in the highest concentrations within the central nervous system in the thalamic-hypothalamic areas, in those regions where it would be expected from the symptoms that these tranquillizers would have their main site of action.

So far, only phenothiazine-derivatives having a similar action to chlorpromazine have been described. All have a side chain in the 10-position, and the 3-position is as a rule substituted. A number of examples are given in Table II. There is some variation in the effect from compound to compound. The potency increases with the following substitutions: $H, CONH{\cdot}NH_2, OCH_3$, $COOCH_3$, Cl, CF_3[102]. The variation is not only quantitative, thus e.g., perphenazine is 7 to 10 times as potent as is chlorpromazine but also qualitative. Comparison between chlorpromazine and triflorperazine shows that the latter is about 3 times stronger when measured by the inhibition of conditioned responses in rats, 5 times as effective in tranquillising monkeys, and 10 times as effective as an anti-emetic[102]. Some clinicians state that the compounds differ in their ability to provoke symptoms of Parkinsonism compared with their clinical effect on psychoses[103,104].

The Minor Tranquillisers

The effects of these compounds are qualitatively or quantitatively less pronounced than those of the major tranquillisers. Nevertheless, they act as tranquillisers; they potentiate the anaesthetic effect of barbiturates and alcohol, and in the clinic they have sedative properties. They also act on functions which have centres in the midbrain and diencephalon, but these actions are weaker or more specialised than those of the major tranquillisers. Some are potent against motion sickness, others have an anti-Parkinsonism effect. Most of them are antihistamines or have been developed from antihistamines. Tables III and IIIA give some examples.

The Hypno-sedatives and the Tranquillo-sedatives

The members of this group are distinguished from the tranquillisers at least in two ways. They have not the specific effect on the same functions with centres in the meso- and diencephalon as have the tranquillisers, and they antagonise convulsants. Some of the products are true hypnotics in

the old sense of the word, giving anaesthesia in sufficiently large doses. The barbiturates, and alcohol, are described in every textbook of pharmacology. Others inhibit the polysynaptic reflexes, and still others have both properties. Table IV gives examples of compounds of this type.

The question arises how the anaesthetic effect and the effect on the polysynaptic reflexes are connected with the sedative properties as measured by the inhibition of motor activity, the synergism with the effect of anaesthetics and the clinical experience. A small correlation of the effect on the polysynaptic reflexes and the sedative action exists. Meprobamate with its well-known depression of the polysynaptic reflexes has also a pronounced and very popular sedative action, but some benzoazoles exert quantitatively a higher inhibition on the polysynaptic reflexes than does meprobamate, and are deprived of a sedative effect[13]. We are perhaps not entitled to include compounds like mephenesin and zoxazolamine among the true psychotropic drugs. Thus it seems indeed as if a red herring rather than a precise knowledge of structure–action relations has led us to compounds like meprobamate.

It is more difficult to decide to what extent the hypnotic action and the sedative action is correlated. It is generally believed that they must be, but the two properties do not follow each other closely. With pentobarbitone, sedation begins at 4 per cent of the LD50, and the anaesthesia is complete at 35 per cent. Phenobarbitone starts sedation at 4 per cent and has a complete anaesthesia at 50 per cent. Finally, with ectylurea a sedation at 1 per cent and full anaesthesia at 90 per cent of the LD50 is observed[105].

Compounds like pentobarbitone and meprobamate differ in their effect. Psychically, alcohol and barbiturates influence the unlearned reactivity less than the learned reactivity while the opposite seems to be true with meprobamate.

As perhaps the psychic action of meprobamate is more like that of the tranquillisers than is the psychic action of the hypnotics, we may distinguish between tranquillo-sedatives for sedatives like meprobamate and hypno-sedatives for sedatives of the barbiturate-alcohol type. However, no sharp line can be drawn between the two types of sedation. Phenaglycodol and presumably many other compounds have traits from both groups[12].

Central Acting Anti-acetylcholines

Benactyzine differs in some respects from the compounds just discussed. It has no sedative action. On the contrary, it increases the spontaneous activity. It has no effect on the unlearned reactivity, as judged for example from the lack of the taming effect on monkeys. It has a stimulating effect on some learned reactions and differs in this way from the tranquillisers. It has also an ability to normalise stress-induced behaviour in some experimental situations. This ability is also found after alcohol, barbiturates and especially after meprobamate. Like all other anti-acetylcholines, for example atropine and hyoscine, benactyzine is a strong inhibitor of the EEG arousal syndrome. The same effect is

also found with the minor tranquillisers which have rather pronounced anti-acetylcholine properties. It is possible that the central effect of benactyzine is connected in some way with its strong anti-acetylcholine effect, but the interrelation is not yet clearly defined. In rats hyoscine, but not atropine, has effects comparable to those of benactyzine[69].

The Older Compounds

The bromides, the lithium salts, and the morphine-like acting drugs are examples of compounds which have not been considered. The reason is that they have not been examined so comprehensively with the same methods as the more recent ones. However, from what we know about them they cannot all be classified in the same groups shown in Table VIII.

Transitional Compounds

The groups presented here seem well defined and differ clearly from each other in their mode of action. Yet, it is easy to find compounds which have properties in common with members of two or more of the here described classes. Thus, as mentioned, phenaglycodol forms a link between the barbiturates and meprobamate.

However, we know of many examples of such "transitional compounds" between groups with little similarity. A recently described compound, 2-(1-*naphthylamino*)-2-*oxazoline* (Table V) is stated to depress the polysynaptic reflexes. In this respect, it belongs to the mephenesin-meprobamate group. It has quieting properties and a taming effect on monkeys. It potentiates the effect of anaesthetics. These properties are common for meprobamate and the major tranquillisers. Finally, it increases the convulsions after leptazol, a property found among the tranquillisers and definitely not characteristic of meprobamate[106]. In this way, naphthylamino-oxazoline forms a link between the sedatives and the tranquillisers as I have classified them in this review.

In addition, at least three examples can be found of compounds which in some respects belong to the sedatives and in others to the stimulants. Apart from its analgesic effect, morphine has some psychic effects similar to those of the major tranquillisers, for example, it inhibits the learned reactivity. On the other hand, it stimulates some lower centres, which generally are inhibited by the major tranquillisers, for example, the trigger zone of the vomiting centre and some of the sympathetic centres.

Azacyclonol[107] is developed from, and chemically closely related to, the stimulating agent pipradrol[108] (Table VII), which has central effects in common with the amphetamines. Azacyclonol is a mild sedative[109], and under experimental conditions its most clearly demonstrated effect is to regulate and normalise the effect of other active compounds. It has been mentioned how it is capable of restoring the constant EEG arousal syndrome provoked by LSD and how it normalises the inhibition of the two neuron intercortical system provoked, for example, by mescaline. It inhibits the motor hyperactivity after amphetamine and pipradrol, but it has no influence on the constant EEG arousal syndrome provoked by

these compounds. In man it is claimed to antagonise the hallucinogenic effect of SD[107,109]. Finally, we may remind ourselves once again how the sedative effect of reserpine and the other indirectly acting tranquillisers may be modified by means of iproniazid to produce the opposite effect; this is now a highly stimulating effect, not unlike that of LSD or the amphetamines. The background of this mechanism of action has already been discussed.

Conclusion

The groups given in Table VIII are merely thought of as a gross characterisation which makes it possible to describe briefly the effect of a well-known or a newly discovered compound. The gradual transition does not allow water-tight compartments into which every compound may be fitted precisely. For this reason it is necessary to determine the "profile of action" covering a long series of effects, similar to those given in Table VIII, if a compound has to be comprehensively described.

In Table VIII, the drugs are roughly arranged from the most depressing to the most stimulating. However, this arrangement does not give a true picture of the mutual relation between the compounds. If attempts must be made to place chemically and pharmacologically related compounds in strict relation to each other, then a multidimensional system is necessary.

Much more important is the interrelation between the pharmacodynamic action and the clinical effect of the compounds. Here our knowledge rests on very rough empirical observations. Only the major tranquillisers are able to ameliorate the major psychoses, the others have an effect only in psychic disturbances of minor, presumably functional, origin, such as the neuroses. In neither the major psychoses nor the neuroses can we expect an effect in every instance. It is not always possible to predict from the symptoms of a psychiatric patient which compound, if any, will have the best prospect of helping. In the development of new drugs we do not even know which property is most important for the required clinical effect. For example, if we want to make a new compound for treatment of schizophrenia—must it be a potent anti-adrenaline, a potent depressor of the extrapyramidal system, a potent depressor of the meso-diencephalic autonomic centres or must it have quite other hitherto unnoticed properties?

Here, the only way to make progress is to correlate as many as possible of the relevant biochemical, physiological, pharmacological, pathophysiological and clinical facts and then hope that we or those who come after us may make something out of them.

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